Environmental Links to Early Deliveries

According to the National Center for Health Statistics, nearly 12% of U.S. babies—more than 460,000 infants—are born prematurely each year, a proportion that has been steadily increasing for about a decade. Research published in the September 2001 issue of the *Annals of the New York Academy of Sciences* associates preterm birth—defined as being born prior to the 37th week of gestation—with 70% of newborn deaths and possibly as much as 75% of newborn health complications. These complications include respiratory problems, bleeding in the brain, infections, and poor growth, all of which can undermine health and development throughout childhood. Some consequences can be lifelong: compared to full-term infants, infants born too soon are at greater risk for conditions such as cerebral palsy, impaired vision, deafness, and mental retardation.

Researchers have sought the causes for preterm birth with the eventual goal of predicting and preventing it. Toward that end, a workshop titled "The Role of Environmental Toxicants in Premature Birth" was sponsored by the Institute of Medicine's Roundtable on Environmental Health Sciences, Research, and Medicine, which in turn is sponsored by the NIEHS. At the meeting, held 2–3 October 2001, presenters reviewed current knowledge about preterm birth and zeroed in on environmental toxicants as a potential risk factor.

"We don't know a lot about what causes preterm birth," admits presenter David Savitz, chairman of the department of epidemiology at the University of North Carolina School of Public Health in Chapel Hill. "From what little we do know, it is very likely that there are multiple contributing factors, and it is very unlikely that we're going to stumble across a single, overwhelming, predominant determinant of this," he says. Additionally, the strongest predictors that have been identified cannot necessarily be remedied, such as a history of prior preterm birth or pregnancies with twins or other multiples. Race and ethnicity, tobacco smoke, and uterine infection may also be predictors, but environmental toxicants have been little explored, says Savitz.

According to Matthew Longnecker, an NIEHS epidemiologist who spoke at the workshop, the first glimmerings that environmental toxicants might factor in preterm birth appeared in two DDT studies in the early 1970s. However, the question was not pursued: "Right about the time that an association between the DDT metabolite DDE and preterm birth was first reported in humans and then in sea lions, the environmental movement had gained enough momentum as a result of [Rachel Carson's 1962 book] *Silent Spring* that it was agreed that DDT should be phased out," Longnecker explains. "It's only recently, in the last ten years, that there has been a steady stream of epidemiologic studies looking at risk factors for preterm birth." The focus on environmental toxicants is even more recent.

A Proliferation of Challenges

Environmental toxicants could potentially be disruptive at any point during pregnancy, each phase of which is regulated by a cascade of hormones and other endogenous chemicals. During pregnancy, certain endogenous chemicals maintain uterine quiescence, or nonactivity. In late pregnancy, others trigger genetic, molecular, and cellular shifts to prepare the uterus for the powerful hormone-driven contractions of birth. Despite intense study, however, knowledge gaps remain with regard to human pregnancy. Chandrasekhar Yallampalli, a professor of obstetrics and gynecology at the University of Texas Medical Branch in Galveston, is one of many researchers seeking to fill these gaps.

At the workshop, Yallampalli described his research focusing on nitric oxide (NO), which may have a role in human uterine quiescence. In animal studies, Yallampalli and his colleagues have shown that NO produced in the uterus during pregnancy maintains quiescence. Disruption of the NO system by environmental toxicants could potentially trigger preterm birth. There is currently no evidence for this, however (researchers aren't even in total agreement that the NO pathway exists in human pregnancy), and Yallampalli notes that a complicating factor lies in translating the results of animal studies to humans, for whom only indirect evidence can be gathered.

There are several big differences between rats and humans with regard to pregnancy, he continues. For example, rats have a high progesterone dependency for maintaining pregnancy, but humans do not. In the same way, NO synthesis may be important in rat pregnancy, but not in human pregnancy. "In humans, there are a couple of studies using nitric oxide . . . to prevent or reduce preterm labor or to prolong the duration of labor once preterm labor has been initiated," says Yallampalli. But these studies do not confirm whether NO actually functions as a quiescent agent in the human uterus, as in the rat uterus.

The animal–human differences extend beyond progesterone, adds speaker Jack Bishop, an NIEHS research geneticist. For example, not only is the length of gestation dramatically different, but rats and mice will resorb fetuses rather than deliver them prematurely. Consequently, the animals that are most easily used in toxicologic testing—rats and mice—are often not the best models for human pregnancy. Other animal models may be more representative, but none are completely ideal.

In epidemiologic studies of pregnancy, the challenges are not unlike those in many other areas of epidemiologic inquiry, says Longnecker. "Many different factors affect risk, and exposures with large effects are the exception—meaning that large studies are needed to detect effects with precision," he says. Characterizing exposure is especially difficult because questionnaires by themselves ascertain only fragments of the information needed, he adds. However, studying pregnancy outcomes has at least one advantage compared with other epidemiologic inquiries: prospective studies are relatively more feasible because of the short time frame of human gestation.

Burgeoning Support from Research

Based on his own and others' research, Longnecker says there is some suggestive, though not conclusive, evidence for environmental toxicants triggering preterm birth. Studies on community-level air pollution suggest a modest association with preterm birth.

In a study published in the 14 July 2001 issue of *The Lancet*, Longnecker and colleagues drew on data gathered through the National Collaborative Perinatal Project between 1959 and 1966 to investigate whether exposure to DDE and preterm birth are related. Through blood sample analysis, the researchers determined DDE exposure of mothers enrolled in the project and compared those results to the gestational age and birth weight of 2,380 of their children. A statistically significant relationship was uncovered, though Longnecker cautions that more research is needed. In line with that need, Longnecker's current research focuses on the effects of DDT/DDE in a highly exposed Mexican population of pregnant women and their offspring.

Another area in which environmental toxicants and preterm birth have been linked is gene–environment interactions. Again, though, caution is advised in reading too much into initial results. "Studying

Preemies and possibilities. New research efforts are examining the potential links between environmental exposures of mothers and developing fetuses and subsequent premature birth.

PhotoDisc

complex gene–environment interactions is a daunting task," warns speaker Xiaobin Wang, an associate professor in pediatrics at Boston University School of Medicine. "The ability of an individual to convert environmental toxicants to less harmful moieties is important for minimizing their adverse health effects," she explains.

This conversion often occurs in two parts: phase I and phase II. Phase I enzymes activate a toxicant, transforming it into an intermediate that is converted by phase II enzymes into an excretable form. Characteristic enzymes of each phase, such as aryl hydrocarbon hydroxylase in phase I and glutathione-*S*-transferase in phase II, are encoded by genes that are highly variable.

As a consequence of this variability, aryl hydrocarbon hydroxylase (encoded by the *CYP1A1* gene) and glutathione-*S*-transferase (encoded by the *GSTT1* gene) work either more or less effectively at clearing toxicant intermediates, depending on the individual. In two studies—one involving benzene exposure, the other tobacco smoke exposure—Wang and her colleagues found significant relationships between preterm birth and certain *CYP1A1* and *GSTT1* variations. "[However,] we have only touched the tip of the iceberg," says Wang of her group's findings. "The issues of genetic susceptibility and gene–environment interactions are only beginning to be explored."

Post-Term Research Endeavors

According to workshop participants, there are many new and continuing explorations ahead. "My ideal goal would be to find some biomarker that we could extrapolate between the rodents and humans," says Bishop. Should such a biomarker be found, testing could be incorporated into current toxicologic protocols. Savitz suggests looking at environmental agents that operate through suspected mechanisms of preterm birth; for example, through some aspect of inflammation demonstrated by infection.

Longnecker adds that epidemiologic data could be gathered through the National Children's Study of Environmental Effects on Child Health and Development, a joint effort of the NIEHS, the National Institute of Child Health and Human Development, the Centers for Disease Control and Prevention, and the U.S. Environmental Protection Agency. "[The National Children's Study] is envisioned as a prospective study, beginning early in pregnancy, of one hundred thousand pregnant women and their families to study the effect of environmental [agents] on the full spectrum of health," Longnecker explains. "While the data to be collected are still being considered, it is anticipated that detailed exposure assessment and collection of biomarkers will allow an especially close look at environmental contaminants and preterm birth, among other outcomes."

Multidisciplinary collaborations will be a vital component for future research. "Until recently, the little bit that has been done looking at environmental factors in preterm birth has mostly been either dismally poor on the environmental exposure assessment or on the assessment of the pregnancy outcome," says Savitz. Studies in this field would benefit from expertise in epidemiology, environmental measurements, toxicology, clinical obstetrics, and biostatistics, he says. Wang adds that other welcome collaborators would have expertise in genetics, molecular biology, bioinformatics, biotechnology, social sciences, and ethics. "The main part that really has to be there is the combined sophistication about the exposure variable and the health outcome variable," notes Savitz.

Workshop participants emphasize that much more work remains to be done. "It's just starting," Bishop summarizes. "This is a major health problem, so it's important enough to try to find some indicators for environmental causes. There does seem to be some validity to the thinking that there may be environmental causes. We just need to get our models better." **–Julia R. Barrett**